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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/083,336	02/27/2002	Mark A. Olson	P67452US0 (RIID 01-58)	8239

7590 04/06/2004

ATTN: MCMR-JA (Ms. Elizabeth Arwine)
Office of the Staff Judge Advocate
U.S. Army Medical Research and Materiel Command
504 Scott Street
Fort Detrick, MD 21702-5012

EXAMINER	
RAO, MANJUNATH N	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 04/06/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/083,336	OLSON ET AL.	
	Examiner	Art Unit	
	Manjunath N. Rao, Ph.D.	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 January 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,7,9,10,14-17 and 24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,7,9,10,14-17 and 24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-5, 7, 9-10, 14-17, 24 are currently pending in this application.

Applicants' amendments and arguments filed on 1-23-04 have been fully considered and are deemed to be persuasive to overcome the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. Specifically Examiner has withdrawn the rejections under 35 U.S.C. § 112, 2nd paragraph in view of the claim amendments.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 14-17 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a pharmaceutical composition comprising ricin polypeptide with SEQ ID NO:1, 2 and variants with SEQ ID NO:3 through 11 having properties such as lacking detectable N-glycosidase-rRNA activity or reduced N-glycosidase-rRNA activity as compared to wild type ricin A, does not reasonably provide enablement for pharmaceutical composition comprising any other variant of the above variants. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1)

the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s).

Claims 14-17 are so broad as to encompass pharmaceutical compositions comprising any ricin polypeptide variant having reduced N-glycosidase activity. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of variants broadly encompassed by the claims. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to the encoded amino acid sequence of only four variants. It would require undue experimentation of the skilled artisan to make and use the claimed polypeptides with an undefined function/activity. The specification is limited to teaching the use of SEQ ID NO: 3-11 as ricin variants having reduced or absent N-glycosidase activity (but probably having other properties such as internalization) but provides no guidance with regard to the making of any type of other variants and mutants or with regard to other uses. In view of the great breadth of the claim, amount of experimentation required to make the claimed polypeptides, the lack of guidance, working examples, and unpredictability of the art in predicting function from a polypeptide primary structure (e.g., see Ngo et al. in The Protein Folding Problem and Tertiary

Structure Prediction, 1994, Merz et al. (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495, Ref: U, Form-892), the claimed invention would require undue experimentation. As such, the specification fails to teach one of ordinary skill how to use the full scope of the polypeptides encompassed by this claim.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass all modifications and fragments of wild type ricin and that of SEQ ID NOS:1-11 because the specification does not establish: (A) regions of the protein structure which may be modified such that it affects activity; (B) the general tolerance of ricin polypeptides to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any amino acid residue with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including variants with an enormous number of amino acid modifications

of the ricin and of SEQ ID NOS:1-4. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of polypeptides having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

In response to the previous Office action, applicants have amended the claims and argue that since claims have been amended, they overcome the enablement rejection. However, it appears that applicants have failed to amend claims 14-17 to overcome the enablement rejection as these claims continue ot be directed to any or all variants of ricin A. Hence while the rejection has been withdrawn for some claims, Examiner continues to maintain the above rejection on claims 14-17.

Claims 14-17 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 14-17 are directed to ricin polypeptide variants having reduced N-glycosidase activity or no N-glycosidase activity with neutralizing epitope and greater solubility compared to wild type ricin. Claims 14-17 are rejected under this section of 35 USC 112 because the claims are directed to a genus of polypeptides including modified polypeptide sequences, modified by at least one of deletion, addition, insertion and substitution that have not been

disclosed in the specification. No description has been provided of the modified polypeptide sequences encompassed by the claim. No information, beyond the characterization of SEQ ID NO:1-11 has been provided by applicants which would indicate that they had possession of the claimed genus of modified polypeptides. The specification does not contain any disclosure of the structure of all the polypeptide sequences including fragments and variants within the scope of the claimed genus. The genus of polypeptides claimed is a large variable genus including peptides which can have a wide variety of structures. Therefore many structurally unrelated polypeptides are encompassed within the scope of these claims. The specification discloses only 4 species of the claimed genus which is insufficient to put one of skill in the art in possession of the attributes and features of all species within the claimed genus. Therefore, one skilled in the art cannot reasonably conclude that applicant had possession of the claimed invention at the time the instant application was filed.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

In response to the previous Office action, applicants have amended the claims and argue that since claims have been amended, they overcome the written description rejection. However, it appears that applicants have failed to amend claims 14-17 in order to overcome the written description rejection as these claims continue to be directed to any or all variants of ricin A whose structure has not been defined. Hence while the rejection has been withdrawn for some claims, Examiner continues to maintain the above rejection on claims 14-17.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-5, 7, 9-10, 14-17, 24 are rejected under 35 U.S.C. 102(b) as anticipated by Huston et al. (US 5877305, issued 3-2-1999), Bernhard(a) et al. (US 5376546, 12-27-1994), Bernhard(b) et al. (US 5416202, May 1995). This rejection is based upon the public availability of printed publications (patents) more than one year before the date of the filing of the instant application. Claims 1-5, 7, 9-10, 14-17, 24 of the instant application are drawn to variant ricin polypeptides having no N-glycosidase or reduced N-glycosidase activity, having neutralizing immunological epitope and a solubility greater than solubility of wild type ricin, an amino acid sequence with SEQ ID NO:3-11 lacking hydrophobic loop made by cleaving the globular domain or, made by recombinant methods and pharmaceutical composition comprising the same and capable of eliciting protective immune response and a kit comprising the same and instructions for use. Huston et al., Bernhard(a) et al., Bernhard(b) et al. independently disclose ricin variants with reduced or absent N-glycosidase activity and comprising amino acid sequence that is 100% identical to SEQ ID NOs:3, 5, or 10 (see enclosed sequence alignments). All above references do not explicitly disclose the polypeptides as having neutralizing immunological epitope and a solubility greater than solubility of wild type ricin as lacking hydrophobic loop.

However, as the reference polypeptides are all derived from wild type ricin and have a 100% amino acid sequence match, Examiner takes the position that all functional characteristics are inherently present in the polypeptides of the reference. All the above references also disclose composition comprising the above polypeptides for therapeutic purposes which the Examiner equates to pharmaceutical compositions claimed in claims 14-17. Therefore, Huston et al., Bernhard(a) et al., Bernhard(b) et al. anticipate claims 1-5, 7, 9-10, 14-17, 24 of this application as written.

Claims 1-4, 7, 9-10, 14-17, 24 are rejected under 35 U.S.C. 102(e) as anticipated by Vitetta(a) et al. (US 20030143193A1, 7-31-03) and Vitetta(b) et al. (US20040009148A1., 1-15-2004). This rejection is based upon the public availability of pre-grant publications of an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent. Claims 1-4, 7, 9-10, 14-17, 24 of the instant application are drawn to variant ricin polypeptides having no N-glycosidase or reduced N-glycosidase activity, having neutralizing immunological epitope and a solubility greater than solubility of wild type ricin, an amino acid sequence with SEQ ID NO:3-11 lacking hydrophobic loop made by cleaving the globular domain or, made by recombinant methods and pharmaceutical composition comprising the same and capable of eliciting protective immune response and a kit comprising the same and instructions for use. Vitetta(a) et al. and Vitetta(b) et al. independently disclose ricin variants with reduced or absent N-glycosidase activity and comprising amino acid sequence that is 100% identical to SEQ ID NO:7 (see enclosed sequence alignments). Both above references do not explicitly disclose the polypeptide as having

neutralizing immunological epitope and a solubility greater than solubility of wild type ricin as lacking hydrophobic loop. However, as the reference polypeptide is derived from wild type ricin and has a 100% amino acid sequence match, Examiner takes the position that all functional characteristics are inherently present in the polypeptide of the reference. Both above references also disclose composition comprising the above polypeptides for therapeutic purposes which the Examiner equates to pharmaceutical compositions claimed in claims 14-17. Therefore, Vitetta(a) et al. and Vitetta(b) et al. anticipate claims 1-4, 7, 9-10, 14-17, 24 of this application as written.

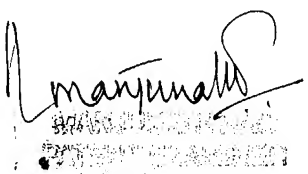
Conclusion

None of the claims are allowable.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Manjunath N. Rao, Ph.D. whose telephone number is 571-272-0939. The examiner can normally be reached on 7.00 a.m. to 3.30 p.m. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy can be reached on 571-272-0928. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-308-4242 for After Final communications. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.



Manjunath N. Rao
April 1, 2004